Association of germline variation with the survival of women with *BRCA1/2* pathogenic variants and breast cancer

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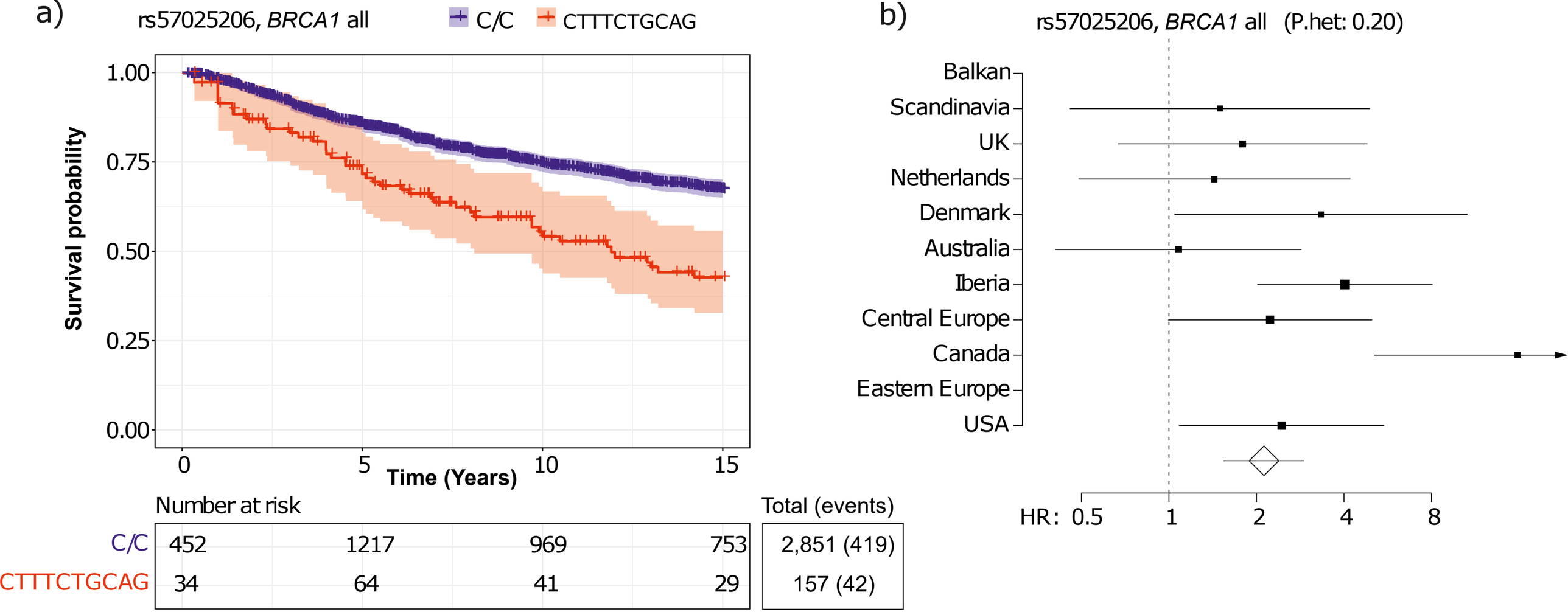
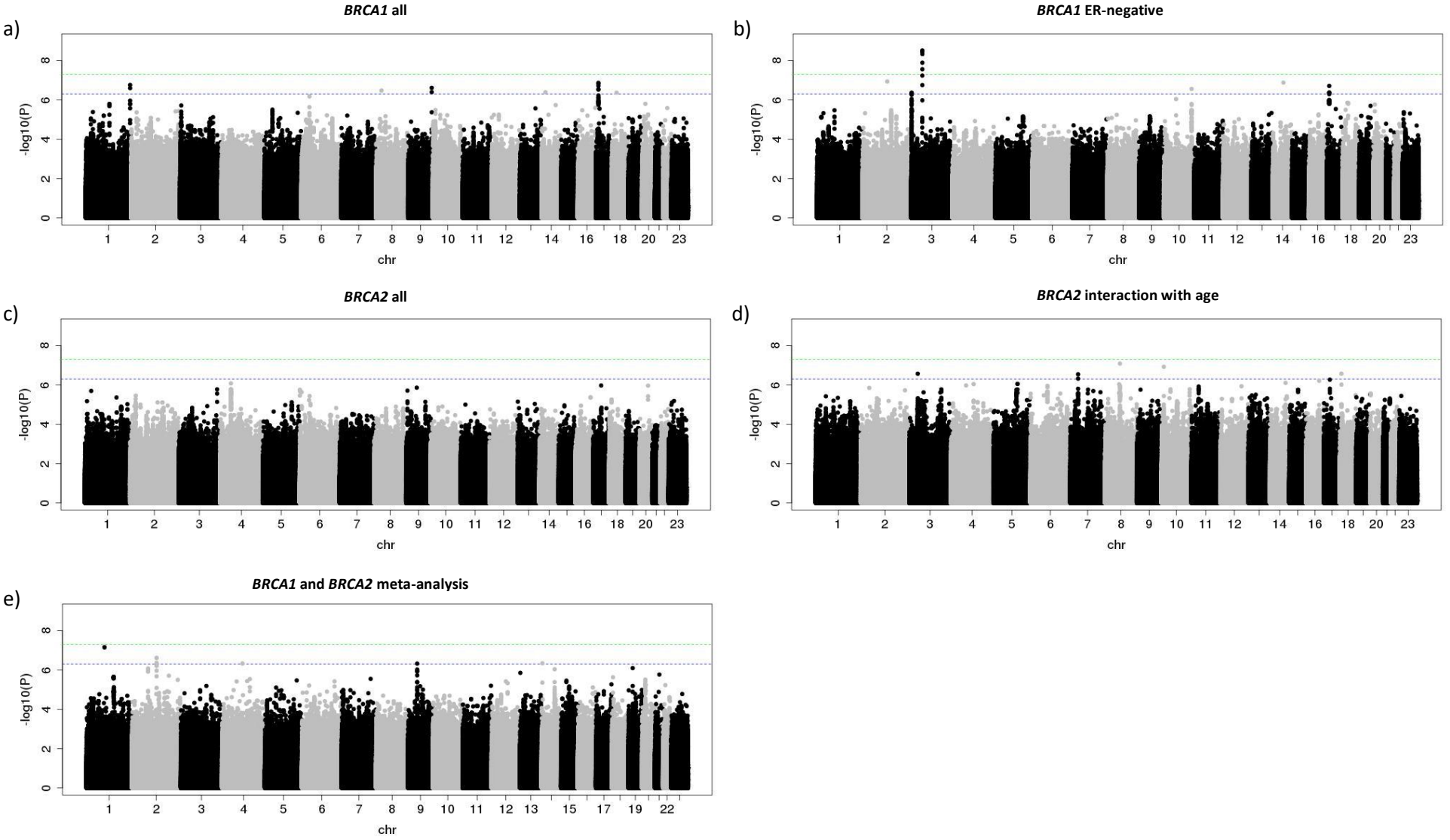
Supplementary Information

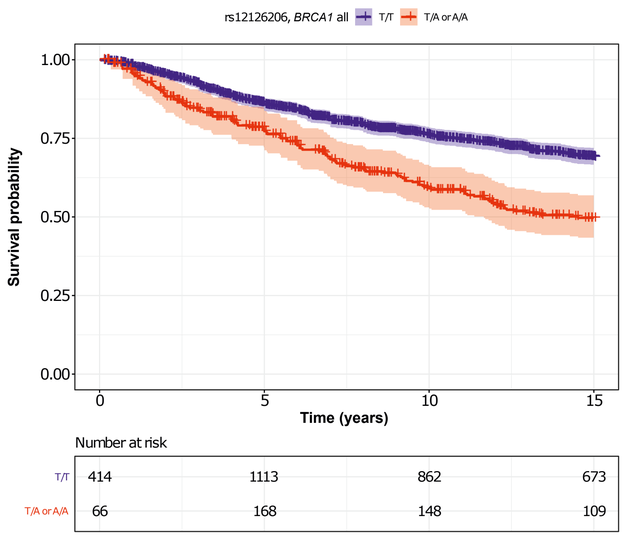


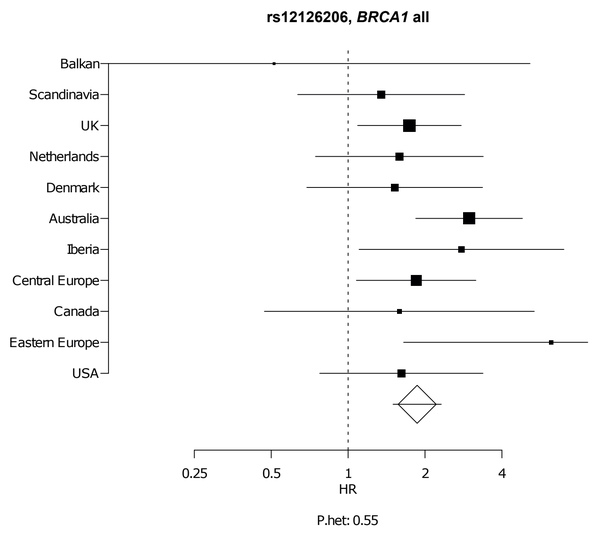
Supplementary Figure 1. The survival effect associated with rs57025206 in all *BRCA1* carriers.
a) Kaplan-Meier plot stratified by rs57025206. b) Forest plot of hazard ratios (HR) accross country groups.
P.het: P-value against between-study heterogeneity.

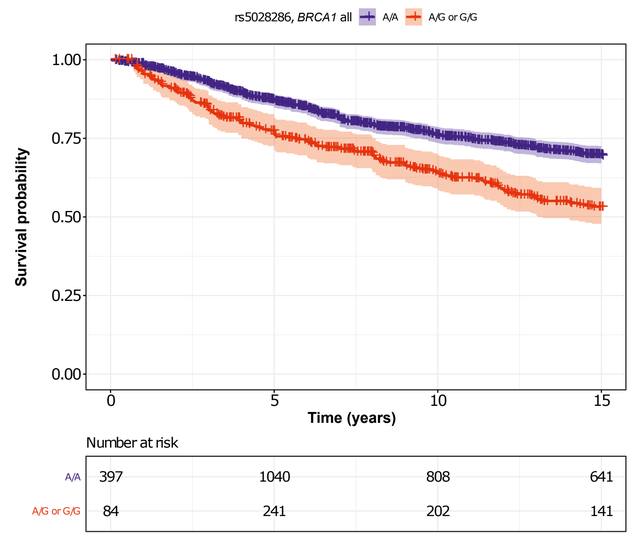


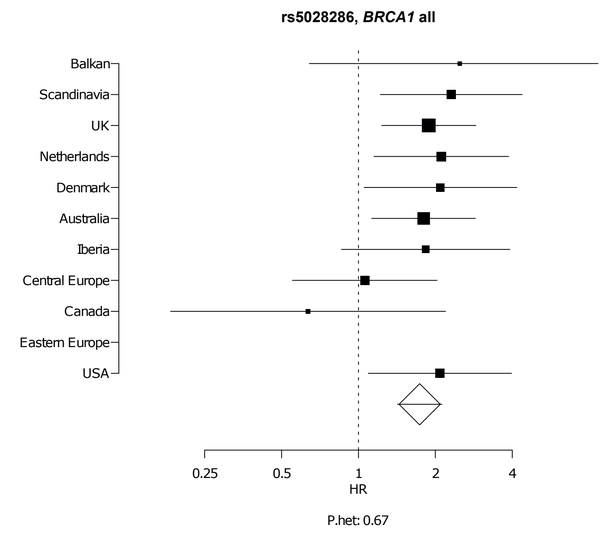
Supplementary Figure 2. Manhattan plots.

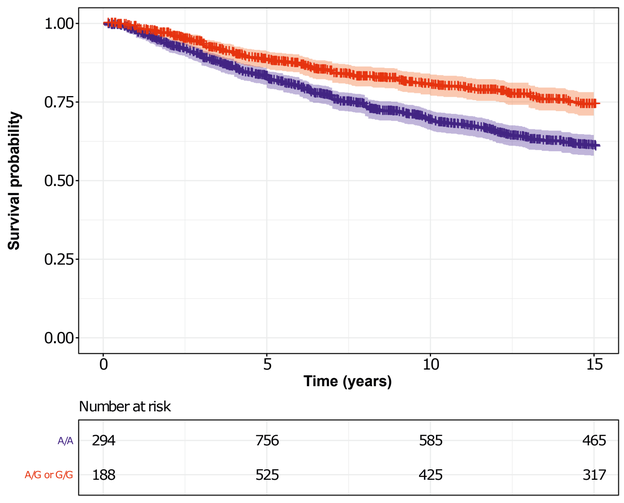
Manhattan plots from survival-association analyses of a) *BRCA1* carriers, b) *BRCA1* carriers with ER-negative breast cancer, c) *BRCA2* carriers, d) *BRCA2* carriers from variant-diagnosis age interaction analysis, and e) a meta-analysis of nominal survival associations in *BRCA1* and *BRCA2* carriers. P-values from likelihood ratio test plotted against genomic position. (Green dashed line: $5 \cdot 10^{-8}$; blue dashed line: $5 \cdot 10^{-7}$)

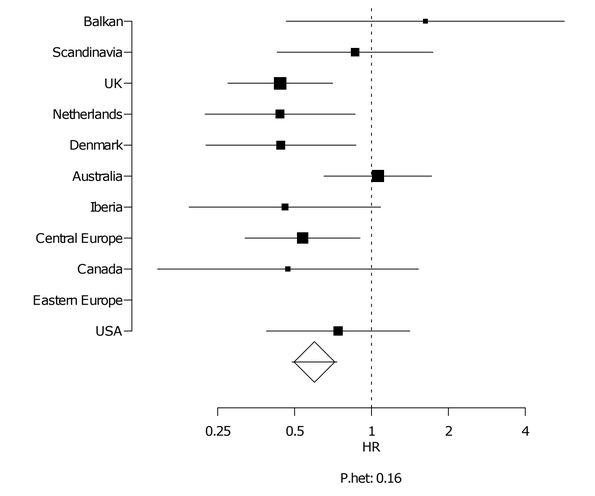


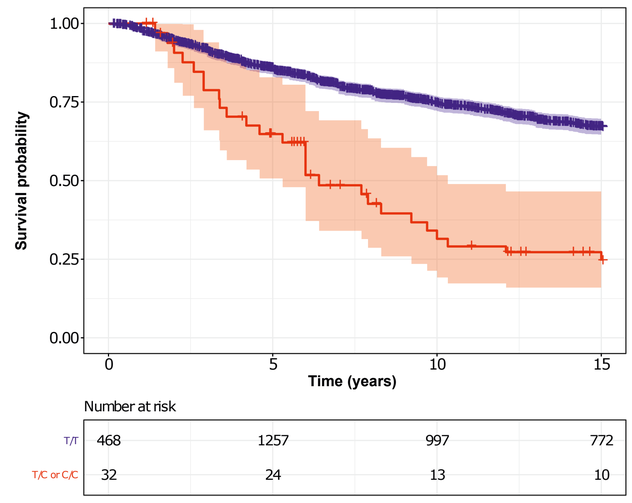


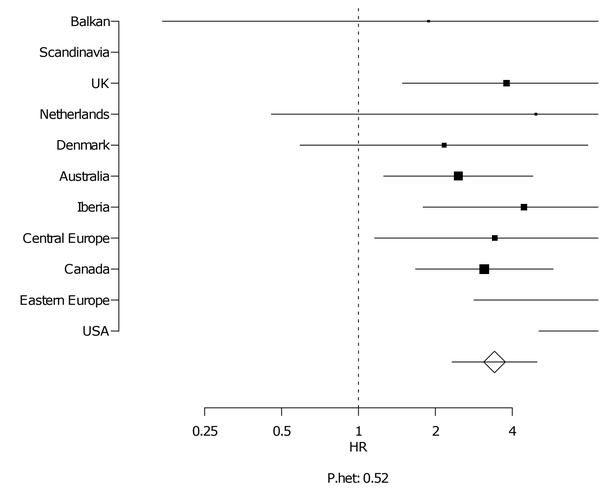


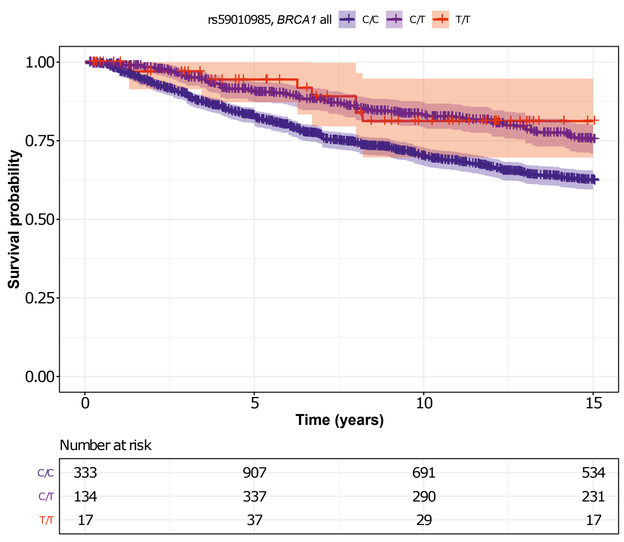


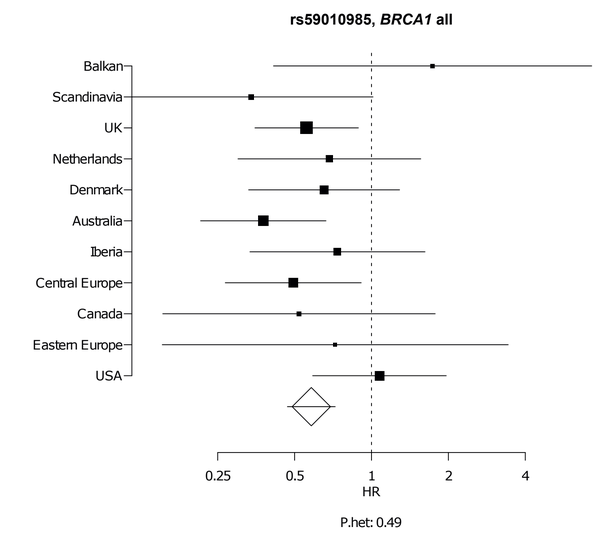


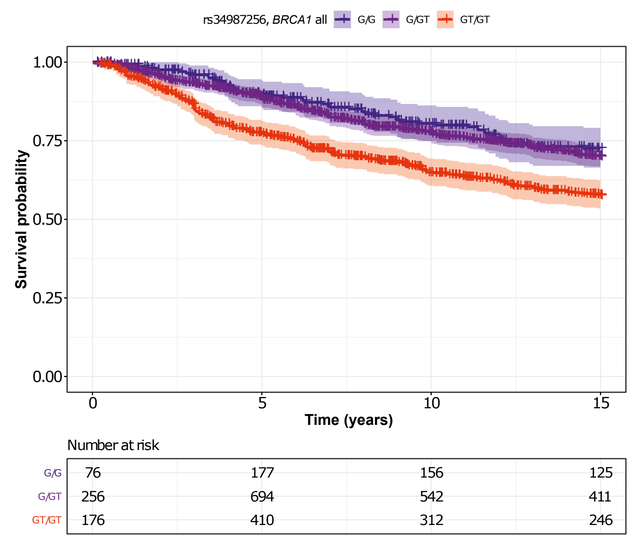


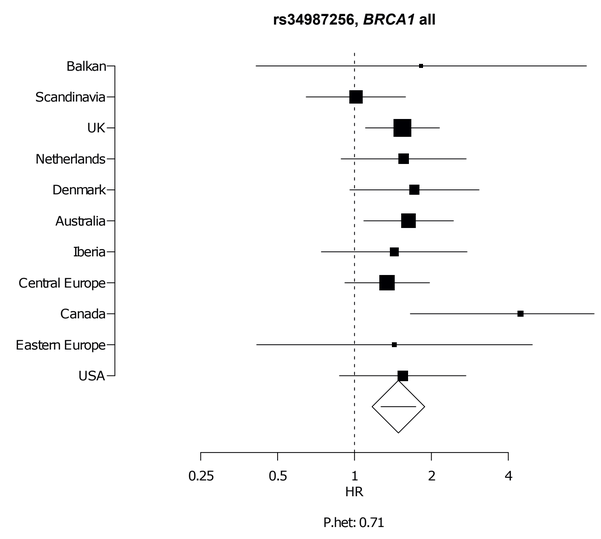


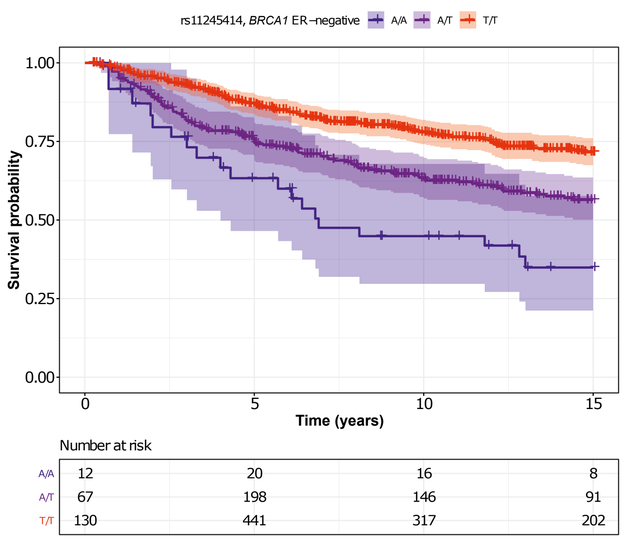


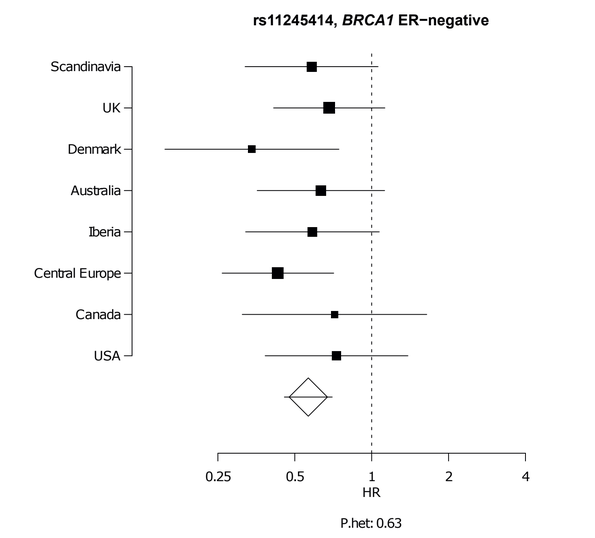


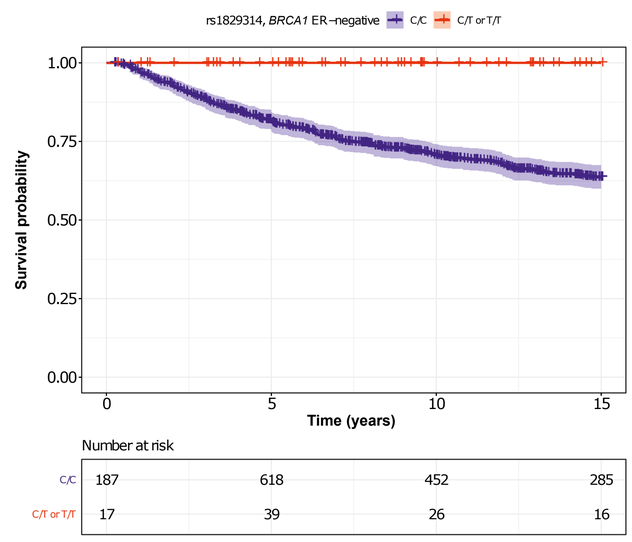


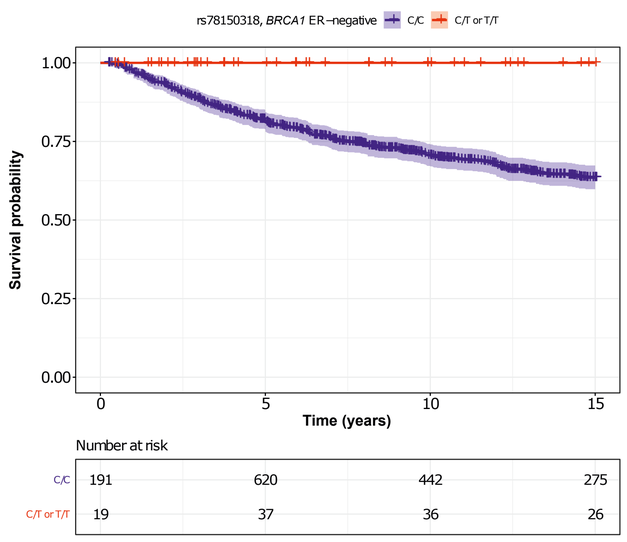




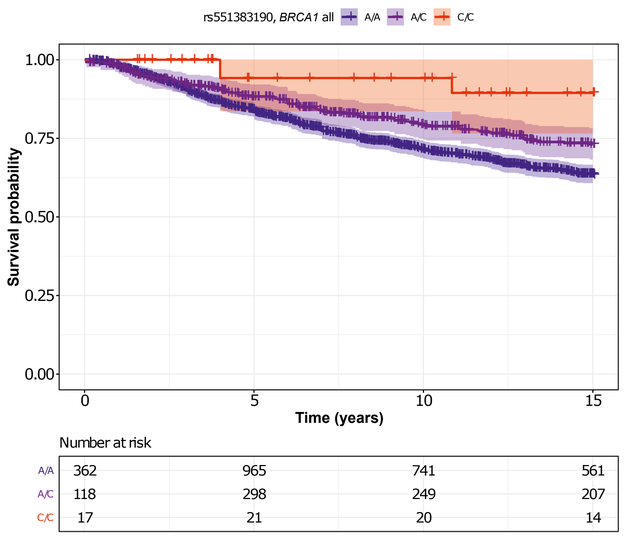


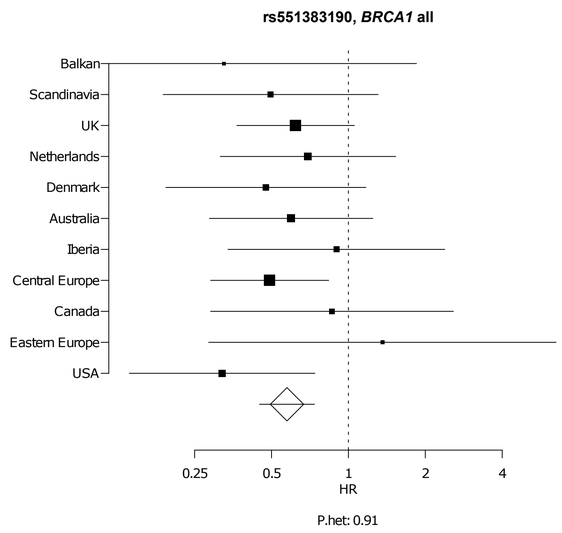


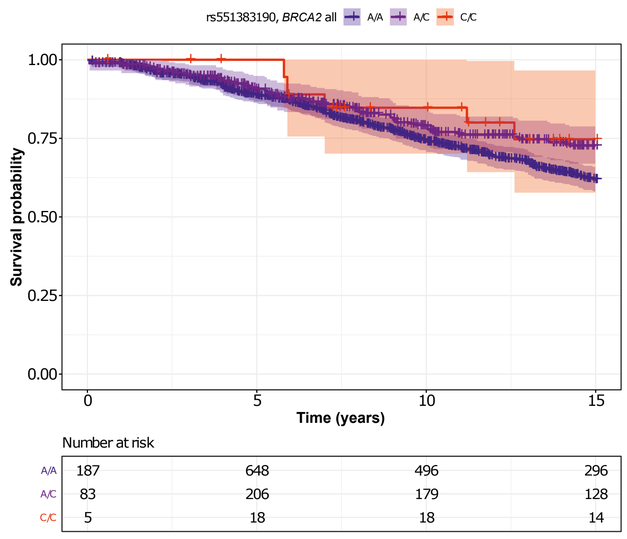


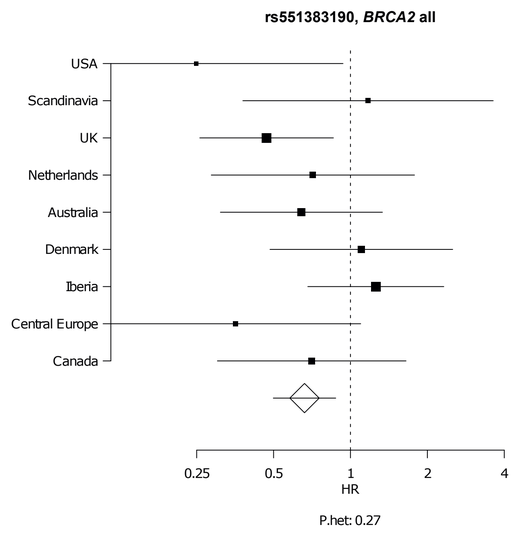


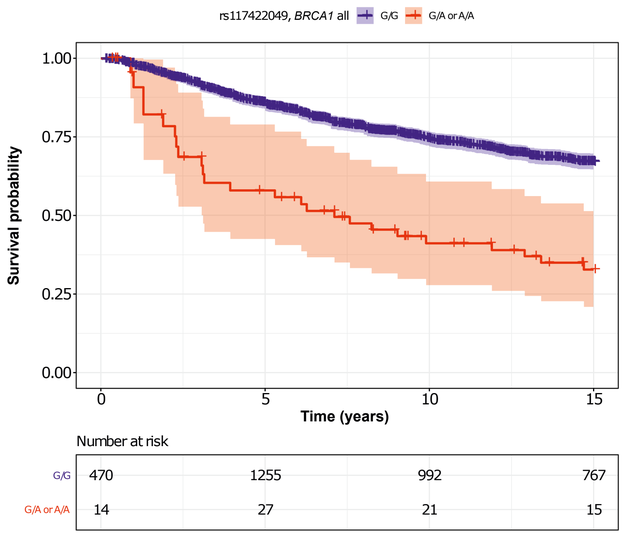
Supplementary Figure 3. Plots for survival variants discovered in *BRCA1* carriers
Kaplan-Meier curves graphically presenting the proportion of surviving patients during the 15 years after primary breast cancer diagnosis in the discovery data (see Table 2), stratified by the 10 *BRCA1*-associated survival variants (1st and 3rd panel from left). Forest plots presenting the effect sizes in different country groups (2nd and 4th panel). Because the carriers of effect alleles of rs1829314 and rs78150318 had no events, the forest plots could not be drawn.

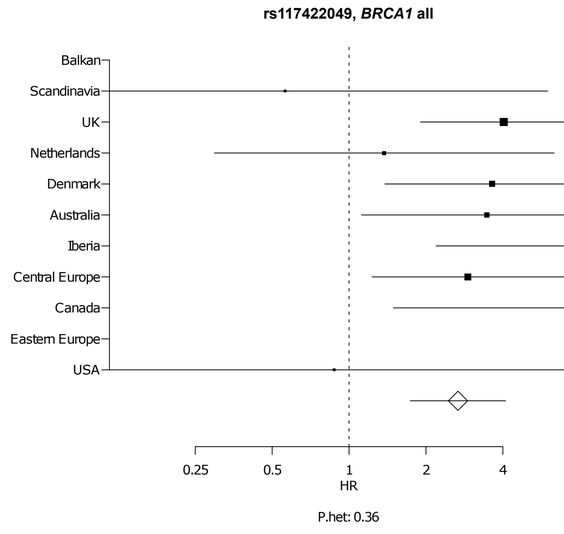


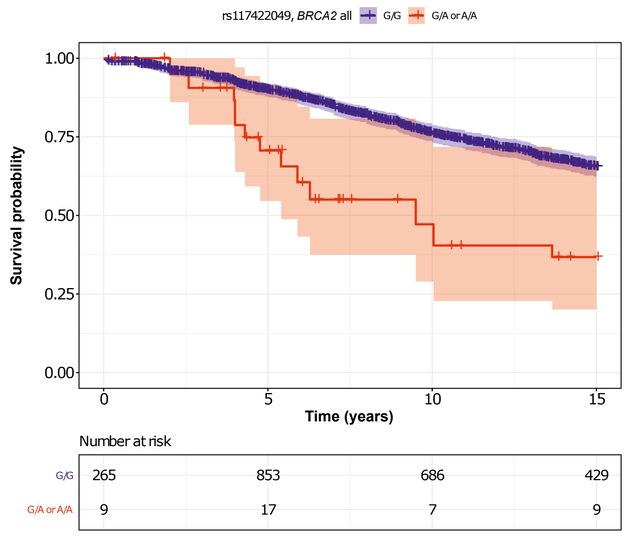


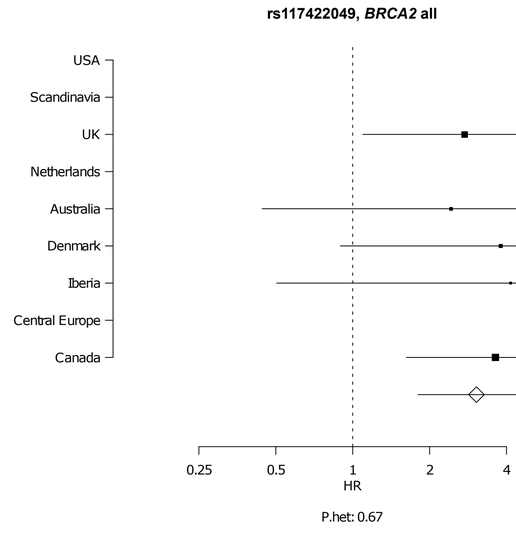


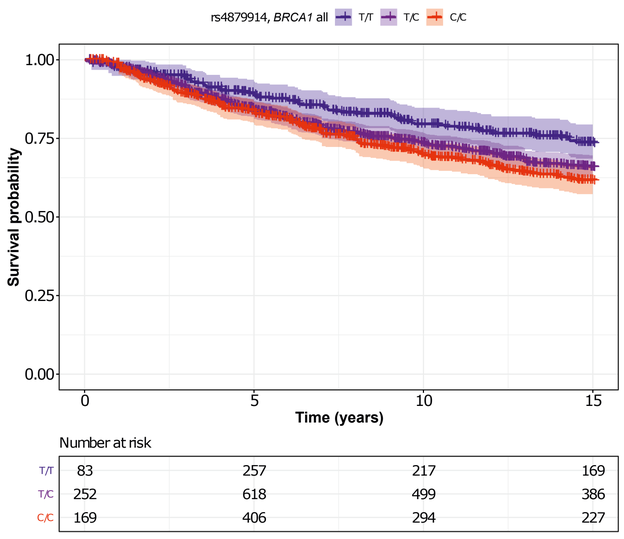


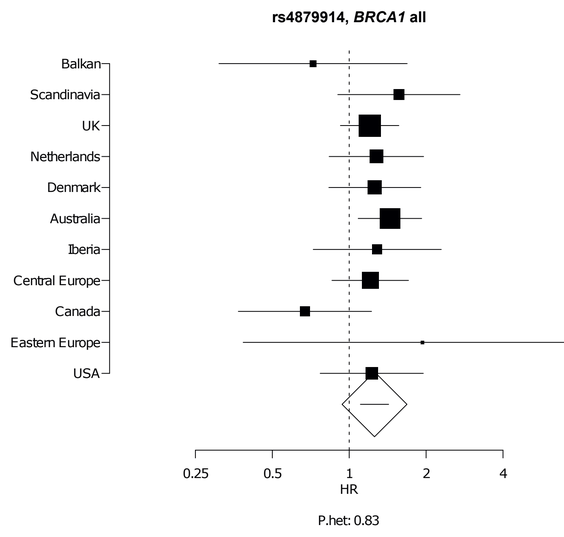


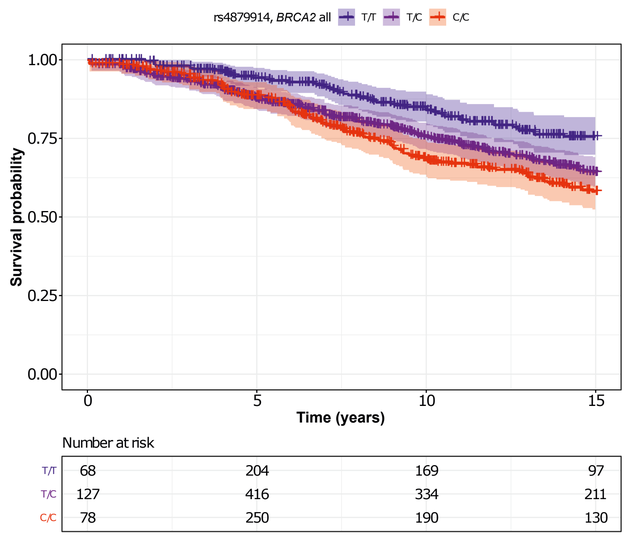


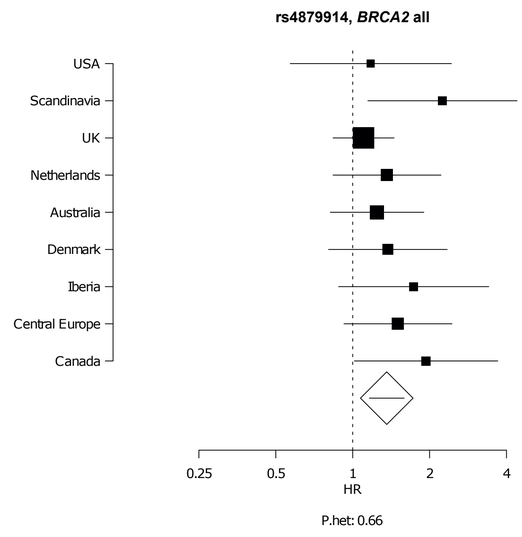


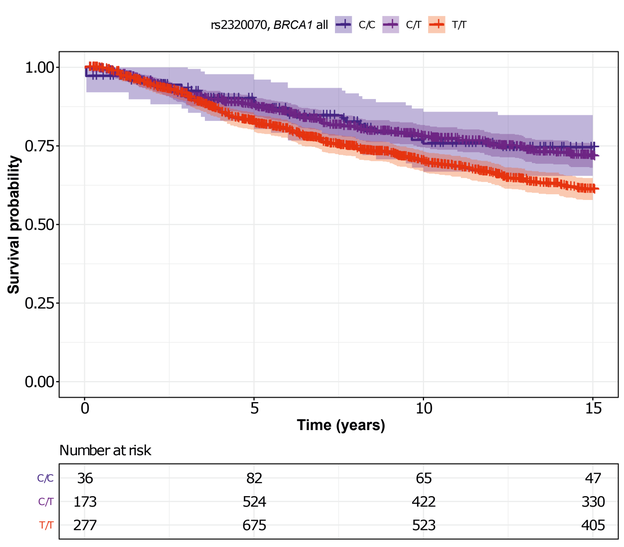


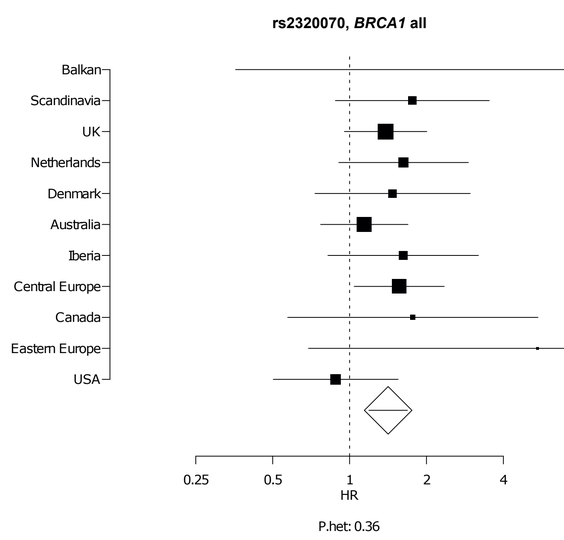


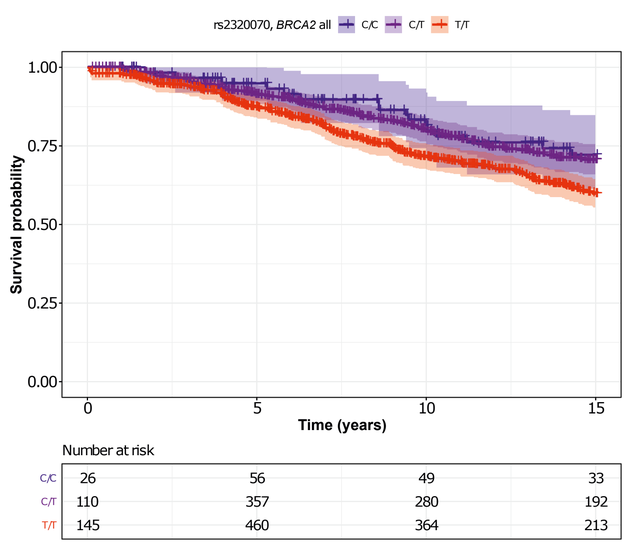


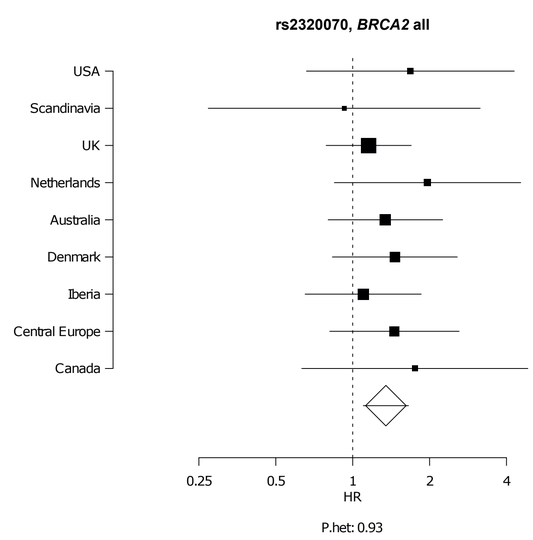




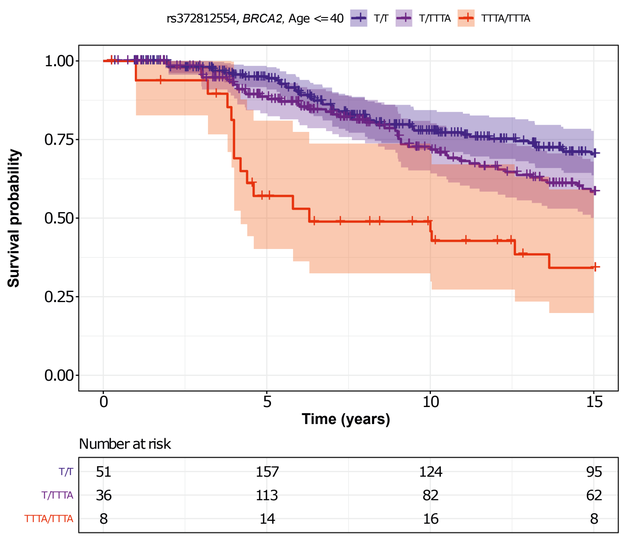


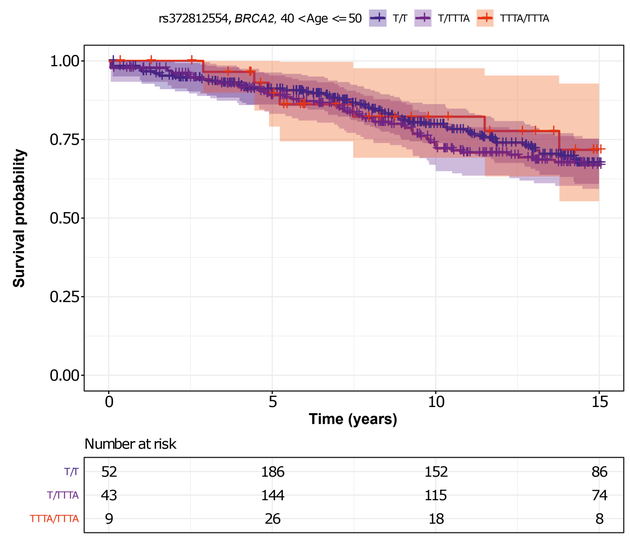


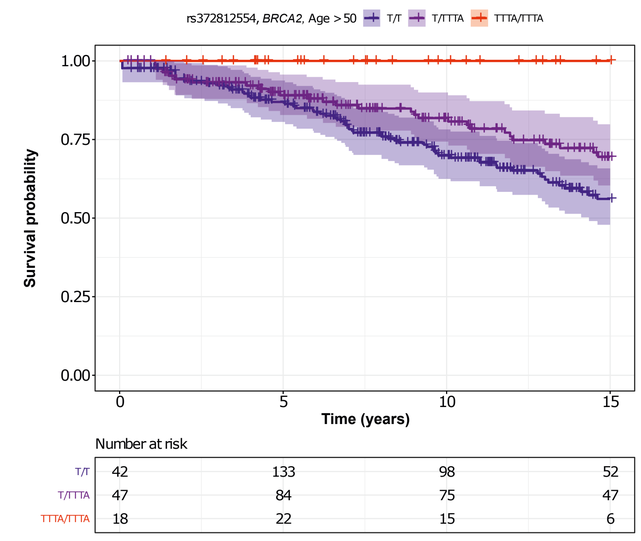


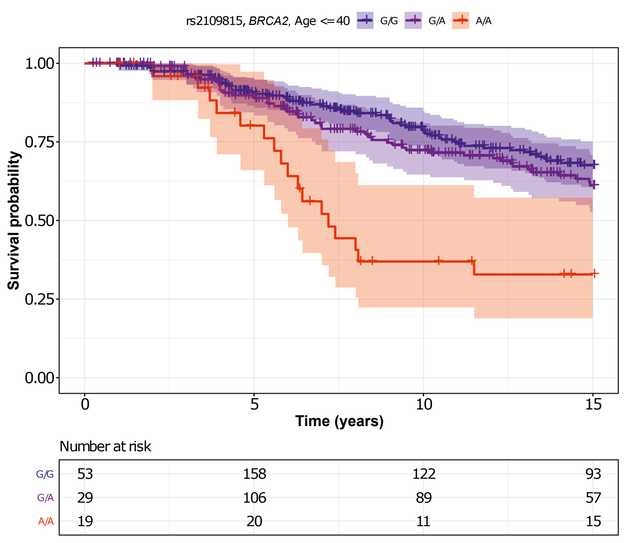


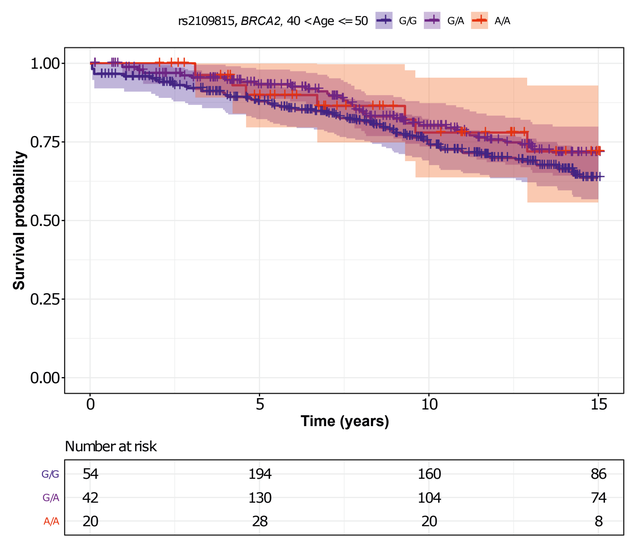
Supplementary Figure 4. Plots for survival variants discovered in the meta-analysis
Kaplan-Meier curves stratified by the four variants with consistent survival effects for *BRCA1* and *BRCA2* carriers (1st and 3rd panel from the left, respectively). Forest plots presenting the effect sizes in different country groups (2nd and 4th panel).

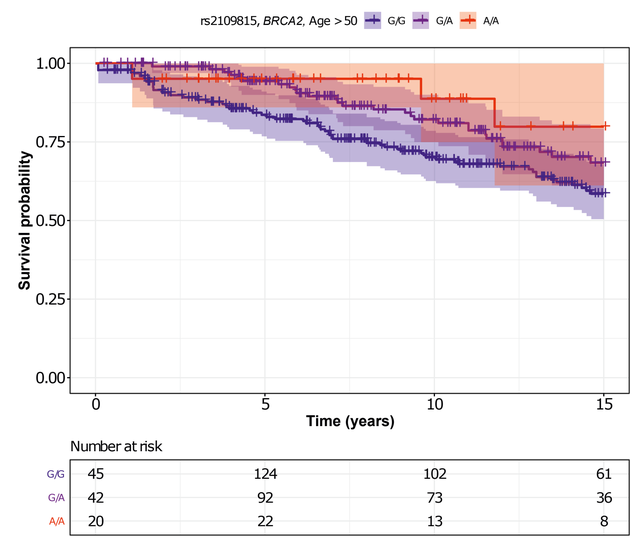


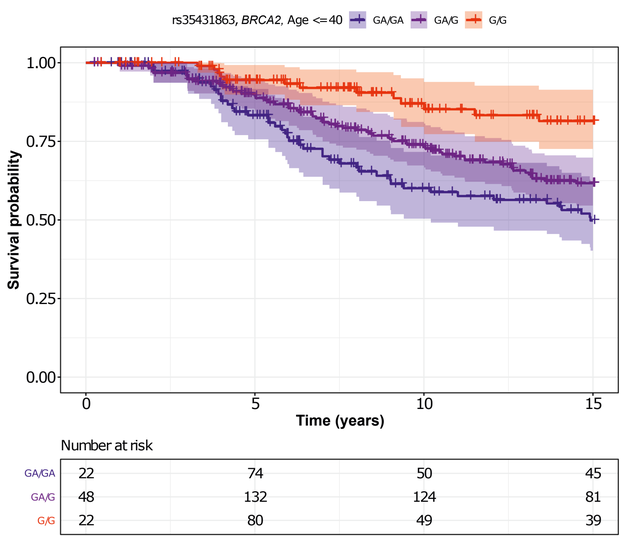


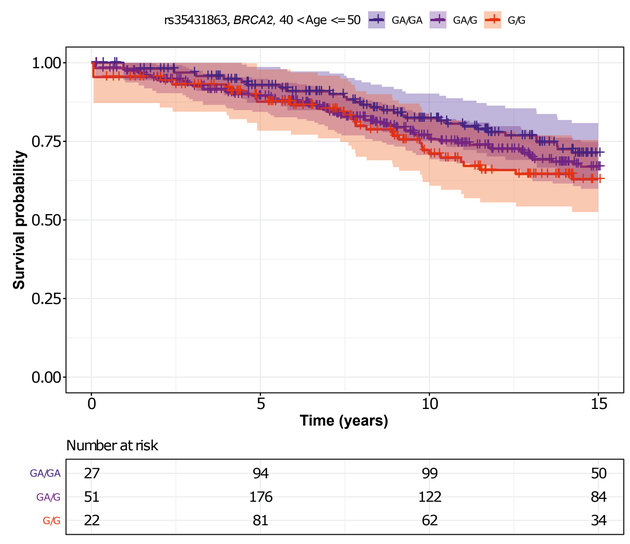


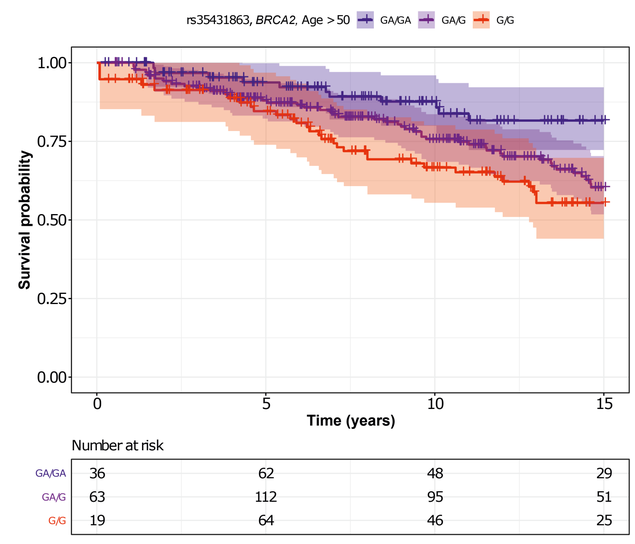


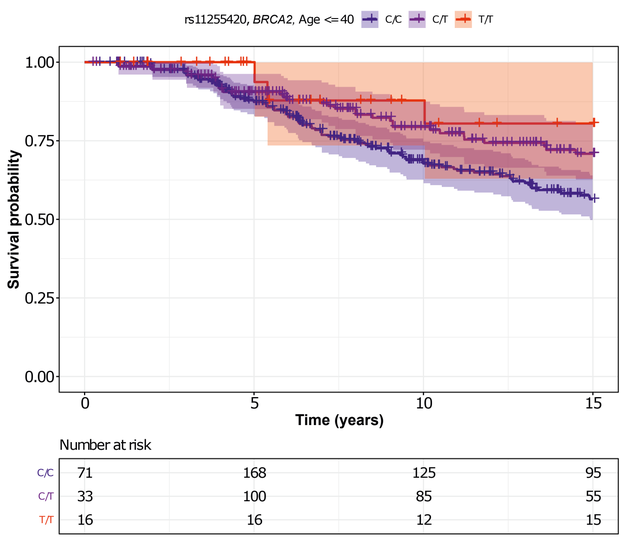


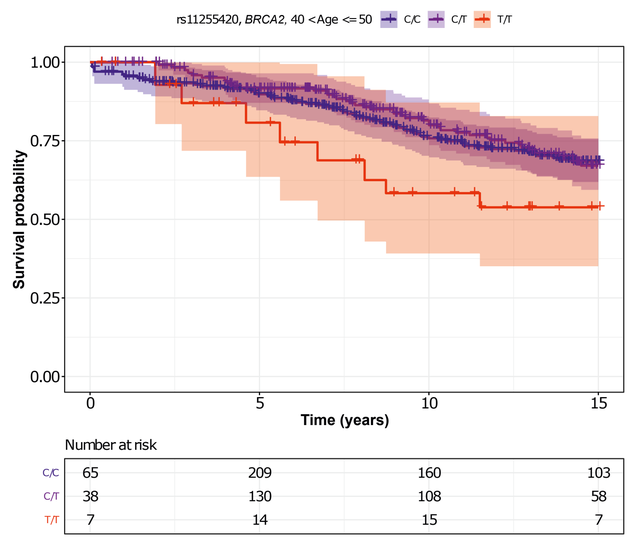


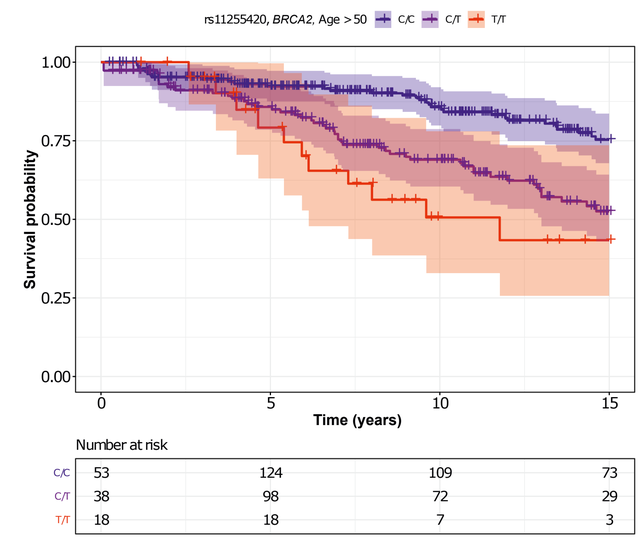












Supplementary Figure 5. Plots for survival variants discovered in *BRCA2* carriers
Kaplan-Meier curves stratified by the four variants with age-dependent survival effect for *BRCA2* carriers in three age-groups: patients diagnosed before the age of 40 years (left), between the age of 40 and age of 50 years (middle), and after the age of 50 years (right).

Supplementary Table 1. Description of CIMBA studies.

Study acronym	Study name	Country	Country group	Study subject ascertainment	Number of study subjects		Number of events	
					BRCA1	*BRCA2*	*BRCA1*	*BRCA2*
BCFR-AU	Australian site of the Breast Cancer Family Registry	Australia	Australia	Population based	25		8	
BCFR-NC	Northern California site of the Breast Cancer Family Registry	USA	USA	Population based	31		6	
BCFR-ON/ OCGN	Ontario site of the Breast Cancer Family Registry/ Ontario Cancer Genetics Network	Canada	Canada	Clinic and population based	73	53	15	17
CBCS	Copenhagen Breast Cancer Study	Denmark	Denmark	Clinic based	73	63	14	9
COH	City of Hope Cancer Center	USA	USA	Clinic based	101		15	
DEMOKRITOS	National Centre for Scientific Research Demokritos	Greece	Balkan	Clinic based	57		9	
DFCI	Dana Farber Cancer Institute	USA	USA	Clinic based	64	46	8	8
EMBRACE	Epidemiological Study of Familial Breast Cancer	UK	UK	Clinic based	694	678	95	89
GC-HBOC	German Familial Breast Group	Germany	Central-Europe	Clinic based	368	207	33	17
HEBCS	Helsinki Breast Cancer Study	Finland	Scandinavia	Clinic based	62	61	18	16
HEBON	Hereditary Breast and Ovarian cancer study the Netherlands	Netherlands	Netherlands	Clinic based	234	93	41	28
ICO	Institut Català d'Oncologia	Spain	Iberia	Clinic based	87	100	14	16
IHCC	International Hereditary Cancer Centre	Poland	East-Europe	Clinic based	94		7	
IPOBCS	Portuguese Oncology Institute-Porto Breast Cancer Study	Portugal	Iberia	Clinic based	39	82	12	11
KCONFAB	Kathleen Cuningham Consortium for Research into Familial Breast Cancer	Australia	Australia	Clinic based	331	245	53	37
MUV	General Hospital Vienna	Austria	Central-Europe	Clinic based	218	108	38	17
OUH	Odense University Hospital	Denmark	Denmark	Clinic based	172	143	30	27
SWE-BRCA	Swedish Breast Cancer Study	Sweden	Scandinavia	Clinic based	97		19	
UPENN	University of Pennsylvania	USA	USA	Clinic based	118	82	13	11
VFCTG	Victorian Familial Cancer Trials Group	Australia	Australia	Clinic based	70	48	13	8

Supplementary Table 2. Additional models for BRCA1 carriers.

Variant effects in multivariate and in breast cancer-specific survival analyses for the SNPs, which were considered novel discoveries in the analysis of *BRCA1* carriers and *BRCA1* carriers with ER-negative breast cancer.

SNP	Analysis subgroup	Genetic model	HR for all-cause mortality in a model adjusted for tumor characteristics		Nominal HR for breast cancer-specific death		HR for breast cancer-specific death in a model adjusted for tumor characteristics	
			HR	[95% CI]	HR	[95% CI]	HR	[95% CI]
rs12126206	BRCA1 all BC	dominant	1.96	[1.37-2.81]	1.53	[1.08-2.17]	1.91	[1.07-3.39]
rs5028286	BRCA1 all BC	dominant	1.55	[1.11-2.17]	1.44	[1.04-1.99]	1.21	[0.69-2.10]
rs736418	BRCA1 all BC	dominant	0.60	[0.43-0.83]	0.72	[0.53-0.96]	0.41	[0.24-0.70]
rs147857072	BRCA1 all BC	dominant	4.95	[2.67-9.18]	2.55	[1.41-4.61]	3.32	[1.28-8.58]
rs59010985	BRCA1 all BC	per-allele linear	0.49	[0.34-0.70]	0.61	[0.44-0.83]	0.66	[0.40-1.09]
rs34987256†	BRCA1 all BC	per-allele linear	1.44	[1.09-1.89]	1.68	[1.31-2.16]	1.61	[1.04-2.48]
rs1829314	BRCA1 ER-negative	dominant	0.00	[0.00-0.00]	0.00	[0.00-0.00]	0.00	[0.00-0.00]
rs57025206	BRCA1 ER-negative	per-allele linear	6.19	[3.73-10.3]	4.68	[2.81-7.80]	4.98	[1.91-13.0]
rs11245414	BRCA1 ER-negative	per-allele linear	0.68	[0.51-0.91]	0.54	[0.40-0.72]	0.63	[0.41-0.97]
rs78150318	BRCA1 ER-negative	dominant	0.00	[0.00-0.00]	0.00	[0.00-0.00]	0.00	[0.00-0.00]

†The hazard associated with the SNP did not significantly violate of the proportional hazards assumption in the multivariate models or in the analyses of breast cancer-associated death.

Supplementary Table 3. Additional meta-analysis models.

Variant effects in multivariate and in breast cancer-specific survival analyses for the SNPs, which were considered novel discoveries in the *BRCA1-BRCA2*-carrier meta-analysis.

SNP	Analysis subgroup	Genetic model	HR for all-cause mortality in a model adjusted for tumor characteristics		Nominal HR for breast cancer-specific death		HR for breast cancer-specific death in a model adjusted for tumor characteristics	
			HR	[95% CI]	HR	[95% CI]	HR	[95% CI]
rs551383190	BRCA1/BRCA2	per-allele linear	0.61	[0.46-0.82]	0.63	[0.49-0.81]	0.68	[0.50-0.94]
rs117422049	BRCA1/BRCA2	per-allele linear	3.43	[0.83-14.3]	3.24	[1.97-5.32]	3.60	[2.00-6.47]
rs4879914	BRCA1/BRCA2	per-allele linear	1.40	[1.18-1.67]	1.39	[1.20-1.60]	1.49	[1.24-1.80]
rs2320070	BRCA1/BRCA2	per-allele linear	1.31	[1.06-1.63]	1.40	[1.17-1.68]	1.46	[1.02-2.09]

Supplementary Table 4. Additional models for BRCA2 carriers.

Variant effects in multivariate and in breast cancer-specific survival analyses for the SNPs, which had age-dependent survival effect for *BRCA2* carriers.

SNP	Analysis subgroup	Genetic model	HR for all-cause mortality in a model adjusted for tumor characteristics				Nominal HR for breast cancer-specific death				HR for breast cancer-specific death in a model adjusted for tumor characteristics			
			dgAge < 40 years		dgAge ≥ 40		dgAge < 40 years		dgAge ≥ 40		dgAge < 40 years		dgAge ≥ 40	
			HR	[95% CI]	HR	[95% CI]	HR	[95% CI]	HR	[95% CI]	HR	[95% CI]	HR	[95% CI]
rs372812554	BRCA2 all BC	per-allele interaction with age	2.11	[1.33-3.34]	0.84	[0.57-1.23]	1.91	[1.32-2.76]	0.74	[0.53-1.04]	2.04	[1.09-3.85]	0.66	[0.39-1.12]
rs2109815	BRCA2 all BC	per-allele interaction with age	1.70	[1.09-2.67]	0.92	[0.64-1.32]	1.78	[1.24-2.56]	0.87	[0.64-1.18]	2.01	[1.17-3.46]	1.12	[0.66-1.91]
rs35431863	BRCA2 all BC	per-allele interaction with age	0.58	[0.29-1.14]	1.29	[0.94-1.78]	0.55	[0.38-0.78]	1.27	[0.98-1.65]	0.62	[0.27-1.44]	1.40	[0.94-2.09]
rs11255420	BRCA2 all BC	per-allele interaction with age	0.62	[0.32-1.18]	1.28	[0.87-1.90]	0.67	[0.44-1.01]	1.73	[1.28-2.33]	0.44	[0.19-1.05]	1.29	[0.74-2.24]

Supplementary Table 5. Survival associations of variants with age-dependent survival effect in BRCA2 carriers, stratified by the tumor ER-status.

SNP	ER-positive BRCA2 carriers (n:1067)		ER-negative BRCA2 carriers (n: 302)	
	under 40 years HR [95% CI]	over 40 years HR [95% CI]	under 45 years HR [95% CI]	over 45 years HR [95% CI]
rs372812554	1.67 [1.19 - 2.36]	0.69 [0.49 - 0.98]	1.43 [0.50 - 4.05]	1.40 [0.77 - 2.54]
rs2109815	1.86 [1.24 - 2.79]	0.75 [0.56 - 1.01]	1.57 [0.84 - 2.93]	0.46 [0.20 - 1.05]
rs35431863	0.54 [0.37 - 0.80]	1.48 [1.15 - 1.90]	0.97 [0.47 - 2.02]	1.31 [0.71 - 2.41]
rs11255420	0.59 [0.41 - 0.83]	1.55 [1.24 - 1.93]	0.47 [0.15 - 1.46]	0.86 [0.43 - 1.69]

Supplementary Table 6. Literature-based functional annotation of the target genes.

Gene	Function		Ref.
KIF26B	silencing in breast cancer cell lines	reduces colony-formation	1, 2
		reduces migration and invasion	
		leads to increased E-cadherin expression and reduced N-cadherin expression	
		induces apoptosis	
		aggregates cells in G0/G1 phase	
	overexpression in breast cancer cell lines	increases proliferation (increased cell count)	2
		promotes migration and invasion	
		positively affects FGF2 expression and secretion	
		leads to MAPK/ERK pathway activation	
	knock-down in a xenograft model	reduces tumor formation	
		reduces the frequency of lung metastases	
	mRNA expression in mammary tumors	is elevated in comparison to adjacent normal	1, 2
	protein expression in mammary tumors	is elevated in comparison to adjacent normal	2
	mRNA expression in breast cancer cell lines	is elevated in comparison to MCF10A non-malignant mammary cells	1
	high expression in mammary tumors	is associated with larger, ER-positive, higher-grade, node-positive tumors, and poor survival	3
	enhances microtubule stabilization	required for asymmetrical cell structure organization and directional migration	4
	mediates multi-drug resistance	in osteosarcoma cells	5
SGCZ	loss in mammary tumors	is more frequent in early-onset tumors (METABRIC)	6, 7
		is associated with poor prognosis	
		does not affect SGCZ mRNA expression in mammary tumors, which is generally very low	
MIR383	is located in intron 1-2 of SGCZ	and MIR383 expression is coupled with SGCZ expression	8
	overexpression in mouse ovarian cells	enhances estradiol release from ovaries via repression of RMBS1, and consecutively also MYC	
	overexpression in ovarian cancer cell lines	sensitizes the cells to paclitaxel	9
RALGDS	is recruited to endosomal compartments	by RILP	10
	mediates the RILP-dependent	inhibition of cell proliferation, migration and invasion	
	serves	as a guanine nucleotide exchange factor for Ral	
	interaction with RILP	affects the MAPK/ERK pathway	
	does not directly stimulate	MAPK/ERK	11
	induces cytoskeletal reorganization	in response to FPR1 stimulation	12
MBIP	was the top-ranking breast cancer risk gene	in a genome-wide pathway analysis	13
GAS7	is hypomethylated (activated)	in ER-negative breast cancer in comparison to ER-positive breast cancer	14, 15
	transcript variant B mRNA expression	is low in mammary tumors in comparison to adjacent normal	16
		is low in early-onset tumors in comparison to late-onset tumors	
		is low in many breast cancer cell lines	
	overexpression in several breast cancer cell lines	reduces proliferation, migration and invasion	
	silencing in MCF-7 breast cancer cell line	increases proliferation, migration and invasion	
	high expression	inhibits actin polymerization via GAS7 – CYFIP1 – Rac1 – WAVE2 complex	
	is regulated by TP53		
	transcript variant B regulatory region	co-localizes with the survival variants (Supplementary Table 5)	
	rs59010985 allele T	is associated with high GAS7 expression (Table 5, Supplementary Table 6)	
	high mRNA expression is associated with	good prognosis of ER-negative breast cancer patients HR = 0.46 [0.37 - 0.58], P = 2.5E-12 (FDR 1%)	17
		good prognosis of breast cancer patients irrespective of ER-status	7
		HR per unit fold change in all 0.81 [0.72 – 0.90], P = 1.4E-4, in METABRIC data	
	mediates the apoptotic effects of	platinum compounds in hepatocellular carcinoma and neuroblastoma cells	18, 19
		gefitinib in non-small cell lung carcinoma	20

Gene	Function		Ref.
CHST9	variant rs1436904	is significantly associated with breast cancer risk in an international consortium study	21
		is associated with survival of triple-negative breast cancer patients in Chinese population	22
		is linked with the survival variant rs537497819 with D'=0.1939, R2=0.0188	
DCAF1	is an E3 ubiquitin ligase substrate receptor	which brings together the substrate and E2 ubiquitin conjugating ligase	23
	recognizes the substrate for ubiquitination	leading to proteasomal degradation of the substrate	
	substrates include	TP53 tumor suppressor, apoptosis regulator	
		ER-alpha via LATS1 interaction	24
		non-histone proteins monomethylated by EZH2 (component of the polycomb repressor complex)	25
	silencing in MCF-7 breast cancer cell line	reduces colony formation	
	regulates	DNA replication	23
		cell cycle progression	
		entry to mitosis	
		cell division	
		ER-alpha level	24
		T-cell activation induced proliferation	26
		T-cell receptor gene reorganization	
		centrosome organization by ubiquitylation as a part of the EDVP complex	27
MIR135A1	deletion in mammary tumors is associated with	higher pathologic stage	28
		younger age of onset	
		ductal histologic type	
		worse survival outcome	
		lower expression of pri-miR-135-a-1, primary precursor of mir-135A1	
	expression in mammary tumors	is higher in ER+ than ER- cancers	
	depletion in breast cancer cell lines	increases cell viability, colony formation, migration, and invasion	
		decreases sensitivity to tamoxifen treatment and contributes to acquisition of resistance	
		enhances the activity of MAPK/ERK and PI3K/AKT pathways	
	forced expression in breast cancer cell lines	decreases cell viability, colony formation, migration, and invasion	
		enhances epithelial cellular phenotype	
		suppresses the activity of MAPK/ERK and PI3K/AKT pathways	
	level is correlated	with epithelial markers	
		inversely with mesenchymal markers	
	forced expression in a mouse model	inhibits tumor formation and lung metastasis	
	promoter is bound by ER-alpha		
	directly binds and regulates ER-alpha	creating a negative feedback loop	
	expression promotes resistance to	oxaliplatin in gastric cancer	29
		gefitinib in non-small cell lung cancer	30
3p21.2 (DCAF1 and MIR135A1)	loss in mammary tumors	is more frequent than loss of any other region in 3p	31, 32
		is associated with high grade and ER-, PR- tumors	
ZRANB1	regulates	EZH2 (component of the polycomb repressor complex) by deubiquitination	33
	silencing in triple-negative breast cancer cell lines	reduces proliferation and migration	
		which can be rescued by overexpressing EZH2	
	silencing in a mouse model	suppresses tumor formation and lung metastases	
	silencing in cell lines	increases stress fibers and inhibits migration	34
	expression in normal mammary tissue	is very low	33
	high expression in mammary tumors	is associated with poor survival	
	is required for	inflammatory T-cell response	35

Gene	Function		Ref.
CTBP2	is a transcriptional co-repressor	and regulator of Golgi apparatus fission	36
	primes target genes	for repression by PRC2	37
	regulates	Aurora B kinase in early mitosis	36, 38, 39
		p16, CDH1, PTEN	
		stem-cell like characteristics of ovarian cancer cells	
	silencing in breast cancer cell lines	leads to TP53-dependent cell cycle arrest and apoptosis	36, 38, 40
		causes cell cycle stasis in aberrant mitosis	
		increases the number of binucleate cells and lagging chromosomes	
		suppresses cell migration	
	overexpression in breast cancer cell lines	increases cell proliferation and cell accumulation in S-phase	38
		decreases E-cadherin expression	
		increases vimentin and MMP2 expression	
	overexpression in a mouse xenograft model	accelerates tumor growth	
	is expressed ubiquitously in	breast cancer cell lines and patient samples	40
	high expression in mammary tumors	is associated with poor survival (ER-negative tumors: HR = 1.72 [1.39 - 2.14], P = 4.5E-7 (FDR 1%))	17, 38
	low expression in ovarian tumors	is correlated with high infiltration of CD33+ myeloid-derived suppressor cells	39
		and poor prognosis of ovarian cancer patients	
	proteasomal degradation can be induced by	APC, UV-light, or cisplatin	40
	may mediate	the immune suppressive nature of KLGR1+ T cells	41
	binds to BRCA1 promoter in ovarian cancer cell lines,	repressing transcription and affecting sensitivity to PARP inhibitors	42
	overexpression reduces sensitivity to cisplatin	in non-small cell lung and esophageal squamous cell carcinoma	43, 44
RAD51B	variant rs2588809	is associated with breast cancer risk	21, 45
		is linked with the survival variant rs78150318 with R2=0.0016, D'=0.4677	
	silencing is associated with	increased genomic instability	46, 47
	somatic alterations in BRCA1-defective breast cancer	are associated with poor overall survival of patients	48
CREB5	is repressed by miR-29c	to inhibit proliferation in a preneoplastic triple-negative breast cancer model	49
	high expression in ER-positive mammary tumors	is associated with good prognosis with HR = 0.61 [0.50 - 0.74], P = 5.7E-7 (FDR 1%)	17
ASPH	locus is amplified in a subgroup of primary tumors		50
	becomes upregulated in response to	IGF1 exposure via MAPK and PI3K/Akt pathways	51
	expression is inversely correlated with	tamoxifen sensitivity of breast cancer cell lines	
	high expression predicts poor outcome	from endocrine therapy for patients with luminal B breast cancer	
	proteins and peptides are highly immunogenic	in induced dendritic cells of hepatocellular carcinoma patients	52, 53
		and may thus be a target for immunotherapy in hepatocellular carcinoma	
GATA3	is a transcription factor		54-56
	regulates differentiation of	mammary gland luminal cells	54, 55, 57
	silencing in mammary luminal cells	blocks differentiation	
		increased proliferation	
		leads to abnormalities nuclear size and orientation	
		causes cell detachment and increased cell death	
	knock-down in mice causes severe defects	in mammary gland formation and lactation	54, 55
	modulates ESR1 binding profile	by enabling ESR1 access to chromatin of limited active histone composition	56
	high expression in mammary tumors	is associated with hormone-positive/luminal tumor phenotype and low grade	58-62
		is associated with good patient prognosis	58, 59, 63-65
		does not affect prognosis	60, 62
		is associated with shorter locoregional relapse time in premenopausal patients	66
		is associated with decreased rate of pathologic complete response to neoadjuvant chemotherapy	61
		is associated with increased probability of GATA3 somatic mutation	65
	regulates spindle orientation	in prostate epithelial cells	67
	has diverse roles	in differentiation and homeostasis of immune cells	68

Gene	Function		Ref.
ZNF644	is a component of G9a/GLP complex	which represses transcription via H3K9 methylation	69, 70
		which interacts with polycomb repressor complex	
		which is a part of the replisome, required to prevent replication-associated DNA damage	
	recognizes the DNA target sequence		69
	silencing in vitro	decreased proliferation	71
		sensitized to replication stress	
		increased DNA damage in replicating cells	
	high expression in mammary tumors	is associated with poor prognosis with HR = 1.43 [1.21 - 1.69], P = 2.2E-5 (FDR 2%)	17
CLASP1	regulates	microtubule dynamics during mitosis	72, 73
	localizes	to the outer region of kinetochore (korona)	
		near the kinetochore-attached microtubule plus-ends	
	knock-down in human and murine cells	leads to chromosomal instability	73
	is required for	invasion through 3D matrix	74
		enhancing compression- resistance of growing microtubules	
	high expression in mammary tumors	is associated with good prognosis with HR = 0.71 [0.63 - 0.80], P = 4.9E-9 (FDR 1%)	17
NIFK	nucleolar protein interacting with the FHA domain	of MKI67	75
	overexpression in ling cancer cell lines	enhances proliferation, migration, and invasion	
	regulates TCF4/β-catenin	via repression of RUNX1 and CK1α	
	high expression in mammary tumors	is associated with poor patient survival	
	is phosphorylated by	CDK1 and GSK3	76
	transcription is induced by	c-Myc and estrogen	
	knock-down in osteosarcoma cell line	induced cell cycle arrest in G1 as a result of ribosomal stress	
	is required for ribosomal RNA maturation	especially in ITS1 (internal transcribed spacer 1) processing	
NIFK-AS1	suppresses macrophage M2 polarization;	M2 polarized macrophages participate in angiogenesis and promote tumor invasiveness	77
	overexpression in macrophages	suppressed the proliferation of estrogen-stimulated endometrial cancer cells	
	high expression in mammary tumors	is associated with good prognosis with HR = 0.64 [0.54 - 0.74], P = 1.5E-8 (FDR 1%)	17
TFCP2L1	is required for pluripotency	of embryonic stem cells	78
	together with Zf5, Ctcf, E2f1, and Myc	predicts the targets of polycomb repressor complex	79
	low expression in mammary tumors	is associated with poor prognosis with HR = 1.41 [1.20 - 1.67], P = 3.1E-5 (FDR 5%)	17
ARHGEF39	overexpression in gastric and non-small cell lung	cancer cell lines induces proliferation, migration, and invasion	80, 81
		increases Akt phophorylation activating the Akt/PI3K pathway	
		increases P38 and ATF2 phophorylation and activates MAPK pathway	
		increases the cellular levels of Cyclin A2, Cyclin D1, and MMP2	
		increases Rac1 activation	
	knockdown in gastric and non-small cell lung	cancer cell lines represses proliferation, migration, and invasion	
TPM2	binds actin	to stabilize microfilaments	82
	in involved in	cytokinesis, cellular vesicle transport, proliferation, migration, and apoptosis	
	expression is reduced	in breast cancer in comparison to adjacent normal tissue	
		in hypoxic conditions	
	silencing in breast cancer cell lines	increases invasion and migration	
		contributes to paclitaxel resistance	
	silencing in HeLa and U2OS cells	induces lysosomal destabilization and lysosomal cell death	83
		sensitizes to cisplatin, siramesine, and etoposide	
	low protein expression in mammary tumors	is associated with poor patient survival	82
	low mRNA expression in mammary tumors	is associated with good survival with HR = 0.64 [0.57 - 0.72], P = 2.9E-14 (FDR 1%)	17

Gene	Function		Ref.
GBA2	Bile acid b-glucosidase	breaks down glucocylceramide (outside lysosomes)	84
	Multi-drug resistant MCF-7	has high levels of glucocylceramide due to high glucocylceramide synthase activity	
	Glucocylceramide synthase repression	increases drug sensitivity in multi-drug resistant MCF-7	
	Overexpression of GBA2	DOES NOT have the same effect in multi-drug resistant MCF-7	
	low expression in mammary tumors	is associated with poor survival with HR = 1.58 [1.35 - 1.85], P = 5.6E-9 (FDR 1%)	17
	silencing leads to accumulation of glucosylceramide	in plasma membrane, affecting actin and microtubule dynamics	85
RUSC2	silencing in lung cancer cell lines	reduced directional migration (chemotaxis)	86
		did not affect random migration (chemokinesis)	
		causes defective Golgi orientation for chemotaxis	
	is required for EGFR-induced	GIT2 (G protein-coupled receptor kinase interacting ArfGAP 2) phosphorylation	
		directional cell migration	
CD72	interaction with CD5 is required for	regulatory B cell and regulatory T cell reciprocal stimulation	87
	is a membrane-bound receptor for CD100	in T cells	88
	interaction with CD100	is required for T cell activation	
TRAV	T cell receptor alpha variable region genes		

Supplementary Table 7. Survival associations in the Breast Cancer Association Consortium (BCAC) data.

Variant	BCAC: analysis group	HR [95% CI]	CIMBA: analysis group	HR [95% CI]	CIMBA: analysis group 2	HR [95% CI]
rs12126206	ER-	0.95 [0.83-1.08]	BRCA1 all BC	1.86 [1.50 - 2.32]		
rs5028286	ER-	1.09 [0.99-1.21]	BRCA1 all BC	1.74 [1.42 - 2.12]		
rs736418	ER-	1.01 [0.93-1.09]	BRCA1 all BC	0.60 [0.49 - 0.73]		
rs147857072	ER-	1.00 [0.67-1.49]	BRCA1 all BC	3.41 [2.32 - 5.00]		
rs59010985	ER-	0.96 [0.87-1.06]	BRCA1 all BC	0.58 [0.47 - 0.72]		
rs537497819			BRCA1 all BC	1.49 [1.27 - 1.74]		
rs1829314	ER-	1.10 [0.92-1.31]	BRCA1 ER-	0 [0 - 0]		
rs57025206	ER-	1.06 [0.86-1.29]	BRCA1 ER-	4.37 [3.03 - 6.30]		
rs11245414	ER-	1.00 [0.93-1.08]	BRCA1 ER-	0.56 [0.46 - 0.70]		
rs78150318	ER-	0.94 [0.78-1.15]	BRCA1 ER-	0 [0 - 0]		
rs551383190			BRCA1/BRCA2	0.61 [0.51 - 0.73]		
rs117422049	All	1.15 [0.98-1.35]	BRCA1/BRCA2	2.80 [1.89 - 4.13]		
rs4879914	All	0.99 [0.96-1.02]	BRCA1/BRCA2	1.30 [1.17 - 1.44]		
rs2320070	All	0.99 [0.95-1.03]	BRCA1/BRCA2	1.39 [1.22 - 1.58]		
rs372812554			BRCA2 under 40y	1.75 [1.33 - 2.31]	BRCA2 over 40y	0.75 [0.59 - 0.96]
rs2109815	ER+	1.03 [0.98-1.08]	BRCA2 under 40y	1.65 [1.24 - 2.19]	BRCA2 over 40y	0.75 [0.59 - 0.95]
rs35431863	ER+	1.01 [0.97-1.06]	BRCA2 under 40y	0.55 [0.43 - 0.71]	BRCA2 over 40y	1.32 [1.09 - 1.60]
rs11255420	ER+	0.98 [0.93-1.03]	BRCA2 under 40y	0.59 [0.41 - 0.83]	BRCA2 over 40y	1.55 [1.24 - 1.93]

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Supplementary note

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Supplementary Data 1. Identification of potential target genes based on variant position and functional annotations. (separate .xlsx file)

Supplementary Data 2. eQTL-analysis in GTEx and Westra et al. data. (separate .xlsx file)